

Review article

Gastric leptin: a putative role in the short-term regulation of food intake

Catalina Picó, Paula Oliver, Juana Sánchez and Andreu Palou*

Department of Fundamental Biology and Health Sciences, University of the Balearic Islands, Palma de Mallorca, Spain

(Received 20 September 2002 – Revised 1 May 2003 – Accepted 25 May 2003)

The discovery of the production of leptin by the stomach, in addition to its production by adipose tissue, has initiated new investigation into the possible role of this protein in the digestive physiology, in particular in the short-term control of energy balance. Leptin has been identified in the lower half of the stomach glands both in the pepsinogen granules of chief cells and in the granules of a specific endocrine cell type, suggesting that leptin action is exerted by both exocrine and endocrine pathways. Gastric leptin is sensitive to the nutritional state, being rapidly mobilized in response to food intake following fasting, or after the administration of satiety factors; this suggests a role for this protein in the short-term regulation of feeding, acting in collaboration with satiety peptides such as cholecystokinin. Leptin, produced by gastric cells and by adipocytes, could act on both acute and chronic regulation of feeding behaviour respectively, giving information to the brain on the availability of external (food) and internal (fat depots) energy resources, thus participating in short- and long-term satiation.

Leptin: Stomach: Food intake: Satiety: Energy balance

The maintenance of an appropriate body weight is very important for the survival of higher organisms. In order to have a constant weight, there must be an energy balance (i.e. energy intake and energy expenditure have to be equal). Evolution has endowed mammals with an integrated, redundant and very complex system for energy control (Woods *et al.* 1998; Palou *et al.* 2000). Despite short-term mismatches in energy balance, energy intake can generally be matched to energy expenditure with great precision due to the existence of several types of signalling biomolecules (such as insulin or leptin) that regulate energy homeostasis, but chronic mismatches lead to changes in adipose mass, which can lead to obesity.

Leptin is a hormone produced mainly by the adipose tissue and it plays an important role in the central regulation of energy balance (Zhang *et al.* 1994). Leptin is released into the circulatory system by the adipose tissue in proportion to the amount of lipids stored and acts in the brain on the leptin receptors, giving information about the size of fat depots (Frederich *et al.* 1995; Maffei *et al.* 1995; Considine *et al.* 1996). As a result of the interaction of this hormone with its hypothalamic receptor, there is a decrease in food intake and an increase in energy expenditure (thermogenesis) (Himms-Hagen, 1999; Ahima & Flier, 2000), helping

the body to maintain the size of its fat depots. Leptin action upon hypothalamic receptors is mediated through changes in the expression of various neuropeptides involved in the central regulation of energy balance: orexigenic neuropeptides such as neuropeptide Y and the agouti-related peptide, and anorexigenic neuropeptides such as proopiomelanocortin and the cocaine–amphetamine related transcript (Palou *et al.* 2000).

Apart from the status of energy stores (fat depots), the expression of leptin by the adipose tissue is influenced by feeding. In human subjects, the release of leptin by the adipose tissue increases after several days of overfeeding, but does not rise in response to individual meals (Kolaczynski *et al.* 1996b), while circulating leptin levels decrease within hours after initiation of fasting (Boden *et al.* 1996; Kolaczynski *et al.* 1996a). The regulation of adipocyte leptin expression by nutrition is probably mediated, at least in part, by insulin, which stimulates leptin expression *in vivo* and *in vitro* (Saladin *et al.* 1995; Rentsch & Chiesi, 1996). These results suggest that leptin produced by the adipose tissue plays a role in the long-term regulation of energy balance (body weight), but is not likely to serve as a short-term meal-related satiety signal (Ahima & Flier, 2000).

Abbreviation: CCK, cholecystokinin.

* **Corresponding author:** Professor Andreu Palou, fax +34 971173184, email andreu.palou@uib.es

Feeding behaviour is, however, a critical aspect for energy homeostasis. Several meal-generated signals or satiety signals accumulate during eating and contribute to meal size. These signals controlling short-term food intake must be integrated in the body's long-term control of energy needs, and there is evidence that the sensitivity of the brain to acutely generated signals is in turn determined, at least in part, by the size of fat mass. Interestingly, it is known that although the adipose tissue is the main source of leptin, leptin is also expressed in the stomach (Bado *et al.* 1998; Cinti *et al.* 2000), and a role of gastric leptin in the control of meal size in cooperation with satiety peptides has been proposed (Cinti *et al.* 2001; Lewin & Bado, 2001). Thus, leptin, a protein produced by the adipose tissue and by the gastric mucosa, may serve to coordinate long- and short-term regulation of feeding behaviour.

Short-term regulation of food intake

In animals, the number of meals per d varies greatly between and within species, and eating schedules can also be modified according to several conditions, such as variable food availability, food types, opportunity, food-associated stimuli, social situations, etc. This implies that energy intake and expenditure are matched to one another despite a considerable variety of eating patterns. Human subjects also enjoy diverse lifestyles, resulting in different eating customs and habits, while maintaining long-term homeostasis. There is also considerable day-to-day variability within individuals as they integrate eating with other activities (Woods *et al.* 2000). This means that there must be a control to determine meal size once eating has begun and to determine the time lag before initiation of a subsequent meal. Consistent with this, the existence of meal-generated signals or satiety factors, together with meal-onset factors, which accomplish this function, is well documented.

Regarding factors stimulating hunger, available results are scarce. In addition to the centrally acting neuropeptides that stimulate hunger and promote weight gain, such as neuropeptide Y (Stanley *et al.* 1986), orexins A and B (also identified as hypocretins 1 and 2) (Sakurai *et al.* 1998), melanin-concentrating hormone (Qu *et al.* 1996), recently, several gastrointestinal peptides including galanin (Yuan *et al.* 2002) and ghrelin (Wren *et al.* 2001a) have been identified as stimulators of appetite (see p. 739).

Patterns of blood glucose and insulin have also been proposed as regulators of feeding behaviour (Campfield & Smith, 2003). In rats, a decline in blood glucose occurs a few minutes prior to initiation of a spontaneous meal, and consistent with this there is a small increase in plasma insulin at the beginning of the premeal decline of glucose (Campfield & Smith, 1990). A similar phenomenon has been reported in human subjects (Campfield *et al.* 1996). Thus, it has been proposed that transient declines in blood glucose are reliable signals for feeding that are detected and recognized by the central nervous system and are mapped into meal initiation in rats and correlated with meal requests in human subjects (Campfield & Smith, 2003).

Satiety factors are molecules responsible for short-term feeding control that provide information to the brain to

inhibit feeding, leading to meal termination, acting centrally via peripheral nerves or via the circulatory system (Woods *et al.* 1998). The most representative of the factors produced by the digestive tract is cholecystokinin (CCK), a peptide secreted during meals that reduces food intake (Gibbs *et al.* 1973). It has specific receptors (CCK_A receptors) located, among many other places, on sensory fibres of the vagus nerve (Moran, 2000). Thus, during a meal, locally secreted CCK can stimulate these nerves and thereby send a signal to the lower brainstem, where they synapse with neurons controlling digestive reflexes and responses, as well as with neurones passing anteriorly to the forebrain (Woods *et al.* 2000). The administration of CCK to rats before the time of food availability causes a dose-dependent decrease in the meal size. Moreover, when selective CCK_A receptor antagonists are administered to animals prior to a meal, meal size is increased significantly (Moran, 2000).

There are also other factors with similar effects, such as gastrin (which is structurally related to CCK), glucagon-like peptide 1 (a peptide produced by post-translational modification of the proglucagon molecule) and the family of the bombesin (bombesin, gastrin-releasing peptide and neuromedin B) (Woods *et al.* 1998), among others. These peptides are produced in response to the presence of food in the gastrointestinal tract.

In addition, there are other kinds of signals that help to limit meal size, including the amount of distension or stretch in the stomach (Phillips & Powley, 1996; Woods *et al.* 2000). The endings of vagal sensory nerves in the muscle layers of the stomach are situated to function as tension or stretch receptors. These nerves have other branches with different kinds of sensory endings, which suggests that two or more kinds of sensory information can be integrated within single vagal neurons (Berthoud & Powley, 1992). The vagal activity elicited by satiety peptides, such as CCK, combine synergistically with that caused by distension of either the stomach or the duodenum (Woods *et al.* 2000).

Satiety peptides can control the size of individual meals; however, various studies show that their repeated administration does not alter body weight. For example, when CCK-8 was administered to rats at the start of each spontaneous meal, the size of each meal was reduced, but the animals compensated by increasing the number of meals per d, and thereby maintained body weight (West *et al.* 1984). Similarly, several studies performed in genetically modified animals also suggest that satiety peptides modulate meal size and induce satiety; however, probably due to compensatory mechanisms activated in knockout animals, some of them maintain normal body weight. This suggests that there are other processes that may compensate for single changes or deficiencies in satiety peptides to maintain the energy balance. For example, CCK_A receptor knockout mice are insensitive to the feeding inhibitory action of exogenous CCK, yet they maintain a normal body weight (Kopin *et al.* 1999). Mice with a targeted disruption of the neuromedin B receptor (Ohki-Hamazaki *et al.* 1999) or of the gastric-releasing peptide receptor (Hampton *et al.* 1998) show normal body weight and feeding behaviour. The targeted gene disruption of the gastric-releasing peptide-1 receptor in mice does not produce obesity

either, although these mutants develop diabetes, showing the importance of glucagon-like peptide-1 in glucose homeostasis (Scrocchi *et al.* 1996).

It is worth noting that in particular strains of rats the lack of a satiety-signalling pathway could result in long-term changes in food intake and body weight. This is the case of the Otsuka Long-Evans Tokushima fatty rats, which have been identified as natural mutants lacking the CCK_A receptor (Moran, 2000). These animals exhibit abnormal insulin secretion in response to glucose administration, do not show decreased food intake in response to CCK administration and are hyperphagic compared with their controls, thus developing obesity and chronic diabetes. The difference between the non-obese phenotype of the CCK_A receptor knockout mouse and the obese phenotype of Otsuka Long-Evans Tokushima fatty rats suggests the existence of additional regulatory factors, but could also indicate that the Otsuka Long-Evans Tokushima fatty rat phenotype may depend on additional genetic alterations.

The gut peptide YY₃₋₃₆, a neuropeptide Y2 receptor agonist, has been recently described as involved in the control of food intake (Batterham *et al.* 2002). Peptide YY₃₋₃₆ is released from the gastrointestinal tract in proportion to the energy content of a meal. In human subjects, peptide YY₃₋₃₆ infusion of normal postprandial concentrations significantly decreases appetite and reduces food intake by 33 % over 24 h (Batterham *et al.* 2002). It has been proposed that peptide YY₃₋₃₆ released in response to food intake may act through the arcuate nucleus Y2 receptor to inhibit feeding in a gut-hypothalamic pathway (Batterham *et al.* 2002), probably acting as a short- and medium-term satiety signal.

Hence, it seems that satiety factors are involved in the control of ingestion in individual meals, but how these actions translate into roles in the overall regulation of energy balance is not clear. Satiety factors must combine with other signals, presumably those proportional to the size of energy stores, such as leptin, and thus the action of meal-related satiety signals can be integrated with long-term adiposity signals. A regulatory loop may also occur in the periphery, since CCK stimulates leptin production by the adipose tissue through activation of an adipocyte gastrin-CCK_B receptor (Attoub *et al.* 1999). Leptin produced by the stomach could also be involved in the early events activated by food intake, as is CCK, being another short-term satiety signal.

Gastric leptin

Leptin was initially described as a hormone specifically synthesized by the adipose tissue and which plays an important role in the central regulation of energy balance (Zhang *et al.* 1994). Adipose tissue is the main source of circulating leptin, but leptin is also expressed in non-adipose tissue sites such as the placenta (Masuzaki *et al.* 1997), mammary epithelium (Casabiell *et al.* 1997), skeletal muscle (Wang *et al.* 1998) and, in particular, the stomach (Bado *et al.* 1998; Cinti *et al.* 2000). The initial view of leptin has been extended to a wider neuroendocrine perspective, being involved in the regulation of a variety of functions,

including metabolism, neuroendocrine and immune function, and development, all of which are related to energy balance, and acting both through central and peripheral mechanisms (Palou *et al.* 2000).

The expression and production of leptin by the human stomach has been described (Cinti *et al.* 2000); there, leptin immunoreactive cells are localized in the lower half of the fundic glands, particularly in the pepsinogen secreting chief cells and also in a specific endocrine cell type, the P cell type, suggesting an exocrine and endocrine way of action for leptin (Cinti *et al.* 2000, 2001). Thus, leptin is probably secreted from chief cells into the stomach lumen and from a special type of endocrine cells into the stomach circulation.

In adult rats, leptin concentration in the stomach was estimated to be half of that found in the epididymal white adipose tissue of rats at the same age (4.61 (SE 0.69) ng/g stomach tissue v. 9.42 (SE 0.53) ng/g adipose tissue; Oliver *et al.* 2002). The concentration of leptin in the human stomach has been reported to be twice (10.4 (SE 3.7) ng/g mucosa; Sobhani *et al.* 2000) that reported for rats, although a direct comparison of available data in human subjects and rats is difficult because of differences in sampling (fundic biopsies in human subjects and the whole stomach or scrapings of the mucosa in rats).

Regulation of gastric leptin production and secretion

There is evidence indicating that feeding stimulates the secretion of leptin by the stomach. In human subjects, it has been shown that leptin is released in response to food intake (Cinti *et al.* 2000): one of the patients in this study, who did not follow the required fasting for endoscopy, had much lower immunostaining for leptin in the gastric cells compared with individuals who had fasted overnight. In rats, gastric leptin is also mobilized in response to food intake (Bado *et al.* 1998; Picó *et al.* 2002). A short food intake stimulus (20 min of refeeding) following fasting is capable of practically emptying the leptin stores from within the stomach mucosa (Picó *et al.* 2002). Intestinal peptides also regulate leptin secretion: in human subjects (Sobhani *et al.* 2000) pentagastrin or secretin administration, and in rats (Bado *et al.* 1998) pepsinogen secretagogues such as CCK, gastrin, or secretin, have been shown to induce gastric leptin release.

Given the unknown properties of gastric leptin, the fact that this hormone is sensitive to the nutritional state, being rapidly mobilized in response to food intake following fasting, or after the administration of satiety factors, suggests a role for this protein in the short-term regulation of feeding, although no conclusive results have been published so far.

Gastric leptin secretion is also stimulated by insulin. In human subjects, insulin administration has been shown to produce a rapid increase in the secretion of leptin into the gastric lumen (Sobhani *et al.* 2002). This effect is dependent on vagal stimulation, since it is produced in patients with intact vagal innervation of the stomach and not in those with selective vagotomy. Pentagastrin stimulation of both gastric leptin and acid output is, however, a direct effect, and does not require the vagus nerve to be intact (Sobhani *et al.* 2002).

The expression of gastric leptin is also stimulated by feeding conditions. In rats, the gastric leptin mRNA level is decreased in fasted conditions and increases rapidly with a short period of food intake (Picó *et al.* 2002). Thus, the increase in leptin mRNA after the food stimulus allows the synthesis of new leptin for the emptying of the stomach stores to be compensated. The regulation of leptin expression appears to be dependent on the functionality of the leptin receptor (Picó *et al.* 2002). Hence, in genetically obese (*fafa*) Zucker rats, which have no functional leptin receptor, leptin mRNA levels in the stomach are up-regulated compared with their lean counterparts, and do not change in response to feeding conditions. Obese Zucker rats also overdisplay stomach leptin levels (Picó *et al.* 2002), as they also have markedly elevated circulating leptin levels (Hardie *et al.* 1996). This might suggest that gastric leptin production is directly dependent on lepR-mediated counter-regulatory mechanisms, or indirectly, depending on other processes altered by obesity *per se*. In obese Zucker rats, however, gastric leptin is also secreted in response to food intake, although the response is relatively lower than in control lean animals (Picó *et al.* 2002), indicating that the functionality of the leptin receptor does not appear to be fully necessary for the stimulation of leptin secretion by the stomach.

The ontogenic pattern of gastric leptin expression and leptin levels in the perinatal period is also in favour of a putative role of this protein in the stomach, probably regulating the ingestive process. An increase in leptin expression in the stomach of neonates is related to the onset of sucking and its production further increases with the change of diet from milk to a solid chow diet (Oliver *et al.* 2002). In addition, gastric absorption of leptin, together with milk fat globules, has been observed in suckling rats, suggesting that leptin could also be transferred from the mother to the infant by the milk, and this could be the main source of leptin in the stomach during the suckling period (Oliver *et al.* 2002). This suggests that gastric leptin could exert biological effects in the neonate, at a time in which both adipose tissue and the appetite regulatory systems are immature (Yuan *et al.* 1999).

Gastric leptin may act on different targets

Gastric leptin could have both central and peripheral actions. Leptin released from the gastric epithelium could go to the blood and act centrally in the hypothalamus, leading to the activation of central processes (involving various neuropeptides). In human subjects, the release of leptin into the blood (after secretin infusion) has been shown to represent an increase in plasma levels of about 25% (Sobhani *et al.* 2000). Other authors (Sobhani *et al.* 2002) have not reported any significant increase in circulating plasma leptin levels after the stimulation of leptin output (either by pentagastrin or insulin). In any case, the increase is probably not large enough to produce a systemic effect as adipocyte leptin does, provided there was a complete chemical identity of leptin from distinct sources, a condition that has not yet been fully proved. Rather, leptin could act by producing local endocrine or paracrine effects (Cinti *et al.* 2001), probably by activation

of nerve endings on the gastric and intestine mucosa. Thus, gastric leptin could provide rapid information to the brain by modulating vagal afferent fibres that originate in the gastric and intestinal walls and terminate in the nucleus tractus solitarius (Yuan *et al.* 1999). Two types of leptin-responsive vagal afferent fibres have been identified (types 1 and 2) with the type 2 requiring CCK-8 for activation (Wang *et al.* 1997), and a synergistic interaction between CCK and leptin, reducing short-term food intake via capsaicin-sensitive vagal afferent has been reported (Barrachina *et al.* 1997). The latter hypothesis is consistent, because CCK_A receptors are present on the vagus nerve (Corp *et al.* 1993); in addition, the long form (Ob-Rb) and one short form (ob-Ra) of leptin receptor transcripts have been identified in the nodose ganglion, which contains the cell bodies of the vagal afferent neurons (Buyse *et al.* 2001b). Thus, leptin could have a genuine effect on satiety, but probably by acting in association with CCK.

In addition, leptin secreted in the gastric juice has the potential to act on luminal targets. Gastric epithelial cells could be direct targets for leptin. In fact, the presence of the signalling-competent isoform of the leptin receptor (Ob-Rb) and short isoforms (more ubiquitously expressed) have been described in the stomach (Tartaglia *et al.* 1995; Wang *et al.* 1996). So far, it is not clear, however, whether activation of these targets involves luminal, endocrine or paracrine pathways, but the presence of a leptin receptor on the basolateral membranes of the epithelial fundic and antral cells has suggested an endocrine and/or paracrine pathway (Sobhani *et al.* 2000).

It must be emphasized that some stomach-derived leptin seems to be stable and not proteolytically degraded in the gastric juice (Sobhani *et al.* 2000). Thus, alternatively, leptin secreted in the gastric juice may reach the intestine in an active form, having biological effects on food digestion and absorption. The functional Ob-Rb isoform of the leptin receptor is also expressed in distinct regions of the small intestine, predominantly in the jejunum and more weakly in the ileum (Morton *et al.* 1998). Different effects of gastric leptin on absorption of various nutrients have already been postulated, including lipids, carbohydrates and proteins. On the one hand, leptin inhibits apoprotein AIV transcription via activation of the jejunal leptin receptor (Morton *et al.* 1998). The apoprotein AIV system serves as a conduit for transport of triacylglycerol as chylomicrons into the circulation and their transfer to acceptor membranes in various tissues. Thus, leptin could play a physiological role in lipid handling on this side, by regulating intestinal triacylglycerol transport (Morton *et al.* 1998). On the other hand, leptin could affect carbohydrate absorption, since it has been shown to induce an inhibitory effect on D-galactose uptake by the small intestine in the rat (Lostao *et al.* 1998). Gastric leptin, however, may enhance absorption of dietary proteins. It has been shown that leptin increases the absorption of oligopeptides via the proton transporter PepT1, by increasing translocation of the cytoplasmic pool of PepT1 to the apical membrane of enterocytes (Buyse *et al.* 2001a). The oligopeptide transporter (PepT-1) provides a major mechanism for protein absorption in the human intestine. An important part of dietary proteins are absorbed as di- and tripeptides rather

than as free amino acids, and this absorption process is carried out by the transporter PepT1 (Adibi, 1997); therefore, the effect of leptin increasing its activity appears to be essential for the efficient absorption of dietary proteins and thus for N supply to the organism.

Some gastrointestinal peptides may work in opposition to leptin

The gastrointestinal peptide galanin may interact with leptin on brainstem neuronal activity

Galanin is a peptide with twenty-nine amino acids; it is widely distributed throughout the central and peripheral nervous system, and the gastrointestinal and genitourinary tracts (Gundlach *et al.* 2001). Galanin mediates a wide spectrum of effects, including stimulation of feeding behaviour (Crawley, 1999). It has been shown that galanin, when applied to the stomach, can activate the peripheral terminals of gastric vagal afferents and modulate physiological action at the brainstem level (Yuan *et al.* 2002). Galanin interacts with other peptides, such as leptin, at the level of the stomach, to decrease afferent neuronal signals to the nucleus tractus solitarius to regulate feeding and energy homeostasis. It has been suggested that galanin could modulate the potency of leptin signals (Yuan *et al.* 2002) that modify food intake. A central inhibitory role for leptin on galanin neurons, which are excitatory to feeding behaviour, has also been shown (Sahu, 1998).

Ghrelin, a gastric hormone involved in appetite, may also work in opposition to leptin

It has been discovered that ghrelin, the natural ligand for the growth hormone secretagogue receptor (Kojima *et al.* 1999), could also be involved in the short- and long-term control of food intake (Wang *et al.* 2002). Ghrelin and its receptor are widespread in the body, but the greatest expression of ghrelin is in the stomach, in endocrine cells located within oxyntic glands (Date *et al.* 2000). The gastric ghrelin is released into the systemic circulation, where its concentration is influenced by acute and chronic changes in the nutritional stage (Ariyasu *et al.* 2001). Stomach ghrelin mRNA levels and secretion (i.e. plasma ghrelin levels) are increased in fasted rats and decreased with re-feeding (Lee *et al.* 2002). Plasma ghrelin is also elevated in human subjects in preprandial conditions and falls after eating (Cummings *et al.* 2001), a pattern reciprocal to that of insulin. These results suggest a physiological role of ghrelin in the regulation of appetite in human subjects, and particularly in meal initiation.

Ghrelin is a very potent stimulant of short-term feeding (Kamegai *et al.* 2001), compared with other orexigenic peptides, and it antagonizes leptin action. Despite being primarily produced by the stomach, ghrelin acts centrally to stimulate food intake. It has been shown that the administration of pharmacological doses of ghrelin rapidly promotes food intake in rodents (Tschöp *et al.* 2000; Wren *et al.* 2001b) and in human subjects (Wren *et al.* 2001a) and also increases weight gain and adiposity in rodents (Tschöp *et al.* 2000; Wren *et al.* 2001b). Its anorexigenic

effects are independent of growth hormone stimulation and appear to be mediated at least in part through activation of neuropeptide Y–agouti-related peptide–neurons in the hypothalamic arcuate nucleus, most of which express ghrelin receptors (Kamegai *et al.* 2001; Shintani *et al.* 2001).

Ghrelin may participate with leptin and insulin in the global regulatory scheme of energy homeostasis. In fact, ghrelin and leptin may be in the opposite site of a system that relays peripheral information to the brain, allowing the maintenance of the appropriate balance between energy reserves and nutritional intake.

Leptin could take part in the system that links short- and long-term regulation of feeding behaviour

When considering the timing of feeding control, two general systems can be distinguished: acute and chronic (Fig. 1). Chronic feeding control depends on leptin released from fat stores. Adipocyte leptin is released into the blood according to the amount of energy stored as fat, and acts centrally by controlling food intake and energy expenditure. This effect requires leptin to cross the blood–brain

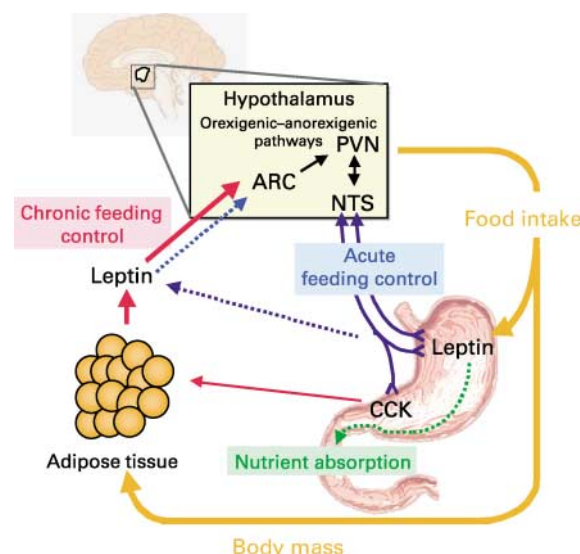


Fig. 1. Schematic diagram summarizing central and peripheral actions of leptin in the short- and long-term control of feeding. Leptin produced by the adipose tissue acts centrally in the hypothalamus, regulating long-term food intake and energy homeostasis through changes in the expression of several orexigenic and anorexigenic peptides. The arcuate nucleus (ARC) is a major site for transduction of adiposity signals into a neuronal response. The paraventricular nucleus (PVN) is supplied by axons from the ARC neurons. In addition, leptin produced by the stomach, together with other gastrointestinal peptides such as cholecystokinin (CCK) involving CCK_A receptors, may act via peripheral vagal afferent pathways that terminate in the nucleus tractus solitarius (NTS) inducing satiety. The processing of the short-term satiety signals in the NTS would result in information transmitted to the PVN, where long-term satiety is also controlled. CCK could also be involved in long-term regulation of leptin production by the adipose tissue through activation of an adipocyte gastrin–CCK_B receptor. Gastric leptin may also be involved in the regulation of nutrient absorption. Leptin may represent a link between acute and chronic control of feeding systems.

barrier and to reach leptin hypothalamic receptors, which in turn modulate the action of a set of brain neuropeptides. The satiety effect induced by circulating leptin is only effective over a long-term period.

On the other hand, acute feeding control that contributes to the short-term satiation after a meal largely depends on satiety peptides released by the stomach while eating, such as CCK. Gastric leptin produced in response to food intake may interact with satiety signals, taking part in the regulation of short-term satiation. Satiety peptides signal the brain through peripheral nerves (vagus afferent fibres) as well as through receptors within the brain itself (Woods *et al.* 1998). This meal-related information is transmitted initially to the nucleus tractus solitarius, a brainstem area that integrates afferent signals arriving from the tongue and the gastrointestinal system, including, in addition to gastric stretch, information on the specific types and amounts of food being processed, or the relative amount of water and solutes (Woods *et al.* 1998, 2000). Afferent neuronal information then passes anteriorly through the brainstem to the hypothalamus (paraventricular nucleus) and other forebrain areas (Woods *et al.* 1998). In the hypothalamus, sensory information from the gastrointestinal tract and taste information from the oral cavity are integrated, together with long-term satiety regulation activated by adipocyte leptin.

In conclusion, leptin, a signalling protein that is produced by adipocytes and by the gastric mucosa, may be a messenger of the availability of external (food) and internal (fat depots) energy resources, which could be used by the brain for both acute and chronic regulation of food intake.

Acknowledgements

This work was supported by the DGI (BFI2000-0988-C06-01 and BFI2000-0988-C06-03) and FIS (FIS01/1379) of the Spanish Government and by the DG Research (COST Action 918) of the European Commission.

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